# Glomerular Filtration

## Introduction

The kidney is designed to filter plasma (blood), to regulate ions, and to eliminate waste. It is the major mechanism for elimination for almost every substance. Biotransformation (metabolism) of drugs and toxins makes them more hydrophilic so that they can be eliminated by the kidney, excreted in the urine (which is water). To do that, the kidneys receive an enormous amount of blood supply (approximately 20% of cardiac output at rest). Most of that blood supply is to do what blood supply does to every tissue—bring oxygen and glucose. The kidney is intensely metabolically active and needs a regular supply of both. But some of the blood supply is meant for filtration.

This lesson is going to focus on the event of filtration at the level of a glomerular capillary. The only focus is how the kidney uses **hydrostatic pressure** to get water and ions from the capillary into Bowman's space (called filtration). Management of ions back into the blood is covered in Kidney #4: *Regional Transport and Pharmacology*. Management of water back into the blood is covered in Kidney #5: *Water*. The filtration barrier, how podocytes restrict the movement of ions, cells, and most proteins, is discussed in detail in Injury #2: *Tubulointerstitial Diseases*.

Accept that only water, ions, and small molecules such as glucose and urea get filtered, and that large proteins such as albumin do not. In normal physiology, filtration has to do with the driving force out of the capillary. The more driving force out of the capillary, the more filtration occurs. The glomerular capillary bed is a **much-higher-pressure** capillary bed than any other capillary bed. This ensures that hydrostatic forces always favor filtration, favor fluid and molecules leaving the capillary bed.

We start with our terminology, then the filtration barrier, then move into the vasculature and filtration forces, closing with the mechanisms that maintain the filtration forces.

## OME Terminology

What follows in this paragraph exists only here at OME. It is designed to help you understand this complex system. There are three values you should be aware of, and only two are named in common medical science—Renal Blood Flow, Glomerular Filtration Rate, and Tubular Blood Flow. We capitalized these to make you think of them as proper nouns and not as common concepts, two "flows" and one "rate." All three represent a volume. **Renal Blood Flow** (RBF) is how much blood—plasma and cells—enters through the afferent arteriole. Renal Blood Flow provides the perfusing pressure that generates the force of filtration and the blood supply to feed the tubule cells. Some of the Renal Blood Flow will be filtered by the glomerulus into the tubules. "Filtered" means fluid from plasma leaves the arterial system into Bowman's space. This volume is the **Glomerular Filtration Rate** (GFR). Whatever volume of blood does not get filtered continues through the efferent arteriole into the tubular capillaries. The amount that doesn't get filtered is **Tubular Blood Flow** (TBF). TBF is our term, which you won't see anywhere else.

This lesson is about the glomerular capillary bed and the forces of filtration. Renal Blood Flow (RBF) brings both plasma and red blood cells. Filtering the plasma means taking things out of the plasma and putting it into the urine. The filtration barrier is designed to prevent filtering of large proteins and cells. Technically, because the barrier of filtration does not permit cells to be filtered, what matters to the glomerulus is **Renal Plasma Flow (RPF)**. We are not going to draw a distinction between RBF and RPF, and will use only RBF.

In the plasma are electrolytes, proteins, amino acids, sugar, and water. About 20% of renal plasma flow will be filtered by the glomerulus. **Filtration** means, "*electrolytes, proteins, amino acids, glucose, and water are pushed out of the capillary and into Bowman's space*." You should consider renal plasma flow and renal blood flow as the same.

## Selective Filtration

The glomerulus filtration barrier and the filtration slits will be discussed in Injury #2: *Tubulointerstitial Diseases*. That lesson describes, in detail, the anatomy of the visceral epithelium of Bowman's capsule, the highly differentiated podocytes, and how they do what this lesson describes. For this lesson, just understand that podocytes act as the filtration barrier—don't get bogged down with the details of how.

The filtration slits ensure that large proteins are not filtered and that only small molecules, such as ions, glucose, and water are filtered. The filtration slits are small (**spatial hindrance**), negatively charged (**ionic hindrance**), and immensely complicated (as discussed in that lesson on glomerular injury).

## Filtration Forces

We covered the normal capillary bed in Cardiology. Every capillary bed has a mixture of oncotic forces and hydrostatic forces generated from the lumen of the vessel and the interstitium outside the vessel. This allows for oxygen to diffuse off the red blood cells, for fluid to be filtered into the tissue at the beginning of the capillary, and also for reabsorption of fluid and carbon dioxide at the end of the capillary. At these normal capillary beds it is about the transition from arteriole to venule. This is true also for the peritubular capillaries that irrigate the tubules of the nephron after the efferent arteriole (more on them in the next lesson).

The **glomerular capillaries** are only meant to filter, to let water, ions, and other small molecules leave the capillary into Bowman's space. Consider what you know about capillary forces already, the elements of the diffusion equation. The permeability coefficient is taken care of by the filtration slits. Only small molecules, ions, and water can filter. There are oncotic forces—albumin and whole cells remain in the capillary lumen, while ions and small molecules are filtered. But those oncotic forces are so small relative to the high-pressure capillary bed that they essentially don't matter. There is a hydrostatic force from Bowman's capsule back onto the capillary. But unless there is an obstruction to urinary flow, that hydrostatic force negligible. Since we're only doing physiology in this lesson, that means the hydrostatic force back from Bowman's capsule doesn't matter. What are we left with? At physiologic conditions, **only alteration of the capillary hydrostatic force changes the glomerular filtration rate**.

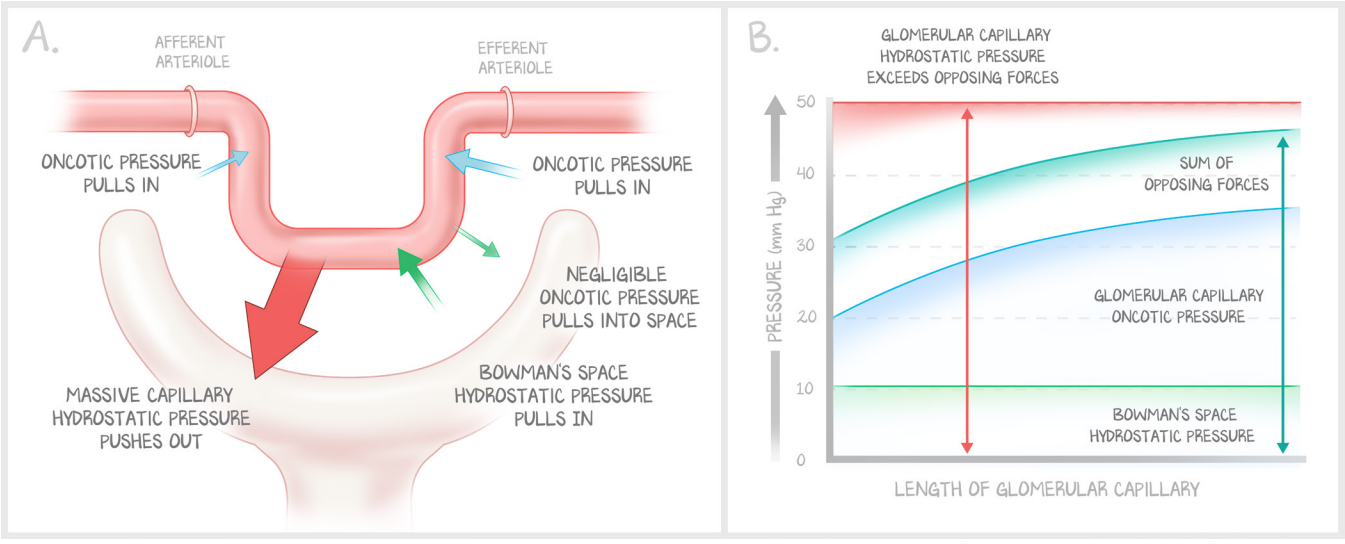


**Figure 3.1: Capillary Forces**
(a) The unique arrangement of the afferent arteriole negates all variables in the diffusion equation except capillary hydrostatic pressure. At the glomerulus, which is under high pressure, because the capillary hydrostatic forces are of such higher magnitude, the others variables have little effect. (b) Graphical representation of the capillary forces. The combination of the oncotic forces pulling into the capillary and the hydrostatic forces of Bowman's space into the capillary are not enough to exceed capillary hydrostatic forces out of the capillary.

The concept of two arterioles scares new learners. It really is quite simple once you master it, but daunting when you start to learn it. The **afferent arteriole** is the arteriole before the glomerular capillary. "Before" in doctor shorthand is the letter "a" with a line over it. A for afferent, A for ante, A for before (and NOT the common error of "AFferrent is AFter"). The afferent arteriole is the arteriole for the glomerular capillary bed. The **efferent arteriole** is the arteriole after the glomerular capillary, at the exit of the glomerulus. More specifically, it isn't the end of the glomerular capillary, it is the arteriole for the peritubular capillary bed. The only thing that happens differently, in comparison to the vascular anatomy of every organ everywhere, is that there is an additional arteriole-capillary relationship (afferent arteriole and glomerular capillaries) in series with the usual arrangement (efferent arteriole and peritubular capillaries). The fact that there are two arterioles in series allows regulation of resistance/pressure/flow into and out of the glomerular capillaries and of resistance/pressure/flow into the peritubular capillaries. The things we need to concern ourselves with are **tubular blood flow** (how much blood gets *past* both the afferent and efferent arterioles) and **filtration pressure** (how much pressure is *between* the arterioles).

We're going to do the garden hose first, then illustrate it with examples of changing the arteriolar tone.

## The Garden Hose

This is a mental exercise designed to use something you are familiar with to explain something that seems really complex. Take the time to visualize the state of the garden hose system at the end of each paragraph.

Connect a garden hose to a faucet outside your house. Turn the water on. The water comes out the end of the hose and onto the lawn. The lawn gets wet. Palm the opening of the hose, hard. You stop the flow of water out of the tube. The lawn doesn't get watered. Remove your hand from the hose. Water flows again.

Put the hose down and walk to the faucet, where the hose is connected and where the valve is. Turn the valve clockwise, shutting off the water. You stop the flow of water into the tube. You have stopped tubular blood flow. Turn the valve counterclockwise, turning the water on. Water flows through the tube and onto the grass. Tubular blood flow is restored. The valve you just turned is the afferent arteriole.

The water on the lawn is tubular blood flow, the blood that makes it to the peritubular capillaries. The end you covered with your hand is the efferent arteriole. The valve at the connection to the house is the afferent arteriole. Tubular blood flow went up (water on the lawn) when you opened the afferent arteriole (faucet) and opened the efferent arteriole (let go). Tubular blood flow went down (no water on the lawn) when you closed the afferent arteriole (faucet) or blocked the efferent arteriole (palmed the opening).

Now connect a different hose. This hose is a floppy distensible hose. Turn the water on high. Water flows through the hose and onto the grass. Now palm the end of the hose to prevent any water from coming out. The water is still on, so water is flowing into the hose, but no water is coming out. What happens to the distensible hose? It distends, the collecting water exerting pressure on the walls of the hose. That's **tubular blood flow**.

For this next part you need a friend. The water is on; you continue to prevent the water from coming out of the hose. The hose is starting to distend. Have that friend take a small nail and poke the hose a few times. The distensible hose has built up pressure in its lumen. When the holes are poked, water shoots out of the holes. The volume of water leaving through the holes is small relative to the amount of water in the hose, and certainly smaller than what would come out if you just unblocked the end.

The poking of those holes created a filtration slit. The water coming out is being filtered. The pressure pushing the water through the holes is the **filtration pressure**. How much water comes out of the holes is analogous to the glomerular filtration rate.

But we're not done. Let your hand off the end of the hose just a little, but not all the way. Water flows out of the hose and onto the lawn, and with alleviated pressure less goes through the holes. Palm the opening again, hard. No water out the end but more out the holes. Let go of the hose entirely and walk over to the faucet again. Letting go of the hose means more water flows out of the hose and less out of the holes, deflating the hose back to its original position.

Turn the water off. No water flows through the hose. No water flows out of the holes.

Flow through the holes is the **glomerular filtration rate**. Turning the water off (constricting the afferent arteriole) or letting go of the hose with your hand (dilating the afferent arteriole) reduces the filtration pressure and thus reduces the water through the holes (decreased GFR). Turning the water on (dilating afferent arteriole) or palming the end of the hose with your hand (constricting the efferent arteriole) increases the filtration pressure and thus increased the water through the holes (increased GFR).

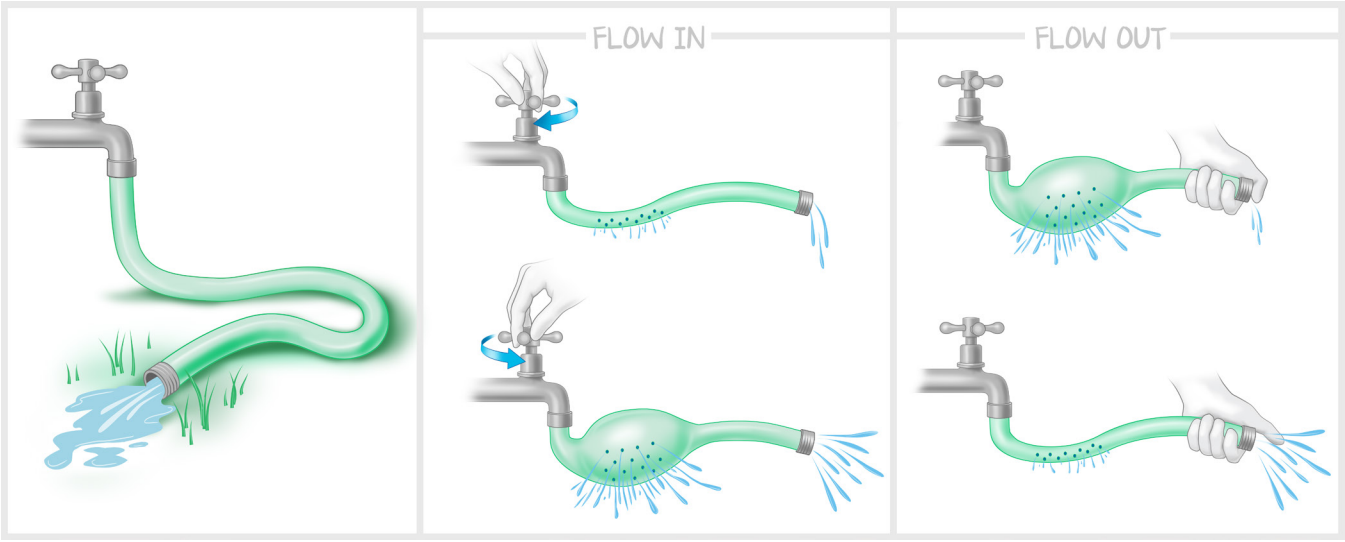


**Figure 3.2: Garden Hose**
A visualization of the text that precedes the illustration, intended to serve as a visual aid while you read.

## Again Using Only Kidney Words

**Tubular blood flow** is how much blood flows past both the afferent and efferent arterioles, and gets to the peritubular capillaries. Tubular blood flow increases with arteriolar vasodilation and decreases with arteriolar vasoconstriction. That is the same thing as every other capillary bed, except now there are two arterioles to consider for the peritubular capillaries. The afferent and efferent arterioles are summative, count as one arteriole, in reference to the tubular blood flow. Things get a little harder for filtration.

**Glomerular filtration rate** is how much plasma is forced out of the glomerular capillary into Bowman's space, how much leaves the vessel lumen (how much water comes out of the holes). It is dependent on the hydrostatic force inside the capillary pushing out. The hydrostatic force inside the capillary is based on flow in and flow out. Hydrostatic forces increase when the garden hose swells, when there is a higher flow rate into the capillary than out (water on, palming the end). Hydrostatic forces decrease either because there is less flow in (faucet closed) or more flow out (hand removed from the end of the hose).

**Flow in** is controlled by the **afferent arteriole**. Constriction of the afferent arteriole reduces the flow into the glomerular capillary and reduces hydrostatic forces (faucet closed). Dilation of the afferent arteriole increases the flow into the glomerular capillary and increases hydrostatic forces (faucet opened).

**Flow out** is controlled by the **efferent arteriole**. Constriction of the efferent arteriole reduces the flow out of the glomerular capillary, causing the capillary to distend, increasing hydrostatic forces (palm the hose). Dilation of the efferent arteriole increases the flow out of the glomerular capillary, causing the capillary to empty, decreasing the hydrostatic pushing force (uncap the hose).

If the afferent arteriole constricts, the resistance through the system increases, and so tubular blood flow falls. If the efferent arteriole remains unchanged, then there is less tubular blood flow to distend the glomerular capillary, and so less hydrostatic pressure, and less glomerular filtration rate. Constriction of the afferent arteriole reduces tubular blood flow and reduces the glomerular filtration rate.

If the afferent arteriole dilates, the resistance to blood flow falls, so tubular blood flow increases. If the efferent arteriole remains unchanged, then there is more tubular blood flow to distend the glomerular capillary, and so more hydrostatic pressure, and more glomerular filtration rate. Dilation of the afferent arteriole increases tubular blood flow and increases GFR.

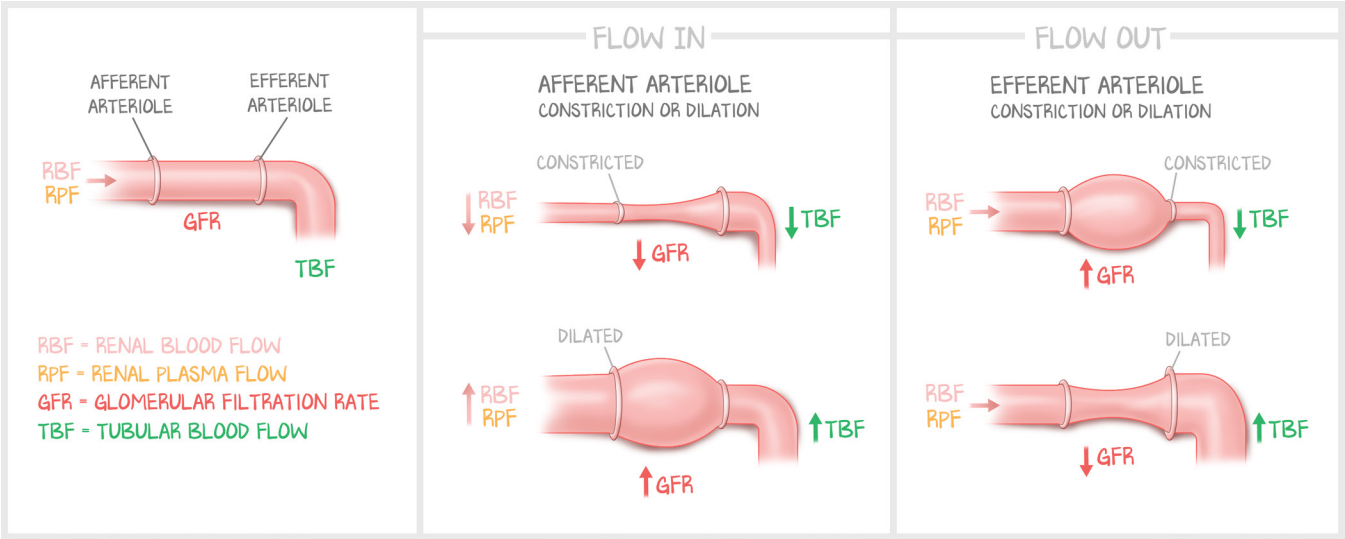


**Figure 3.3: How Alterations in Arterioles Alter GFR and TBF**
The afferent arteriole controls flow into the glomerular capillaries and therefore also influences flow out of the capillaries. Constriction of the afferent arteriole reduces RBF, which in turn reduces both GFR and TBF. Dilation of the afferent arteriole allows more RBF, increasing both GFR and TBF. The efferent arteriole controls only flow out of the glomerular capillaries. Constriction of the efferent arteriole reduces the blood out, so increases GFR but reduces TBF. Dilation of the efferent arteriole increases the blood out, so reduces GFR and increases TBF.

## Regional Hydrostatic Pressure, Autoregulation

In Cardiology, we learned that the oxygenated capillary hydrostatic pressure decreases across the length of the capillary, so that on the venule side there is very little hydrostatic pressure. So little that the venule side of the capillary shows net absorption. This does not happen in the glomerulus. The afferent arteriole maintains substantial pressures across the glomerular capillaries such that only filtration is favored.

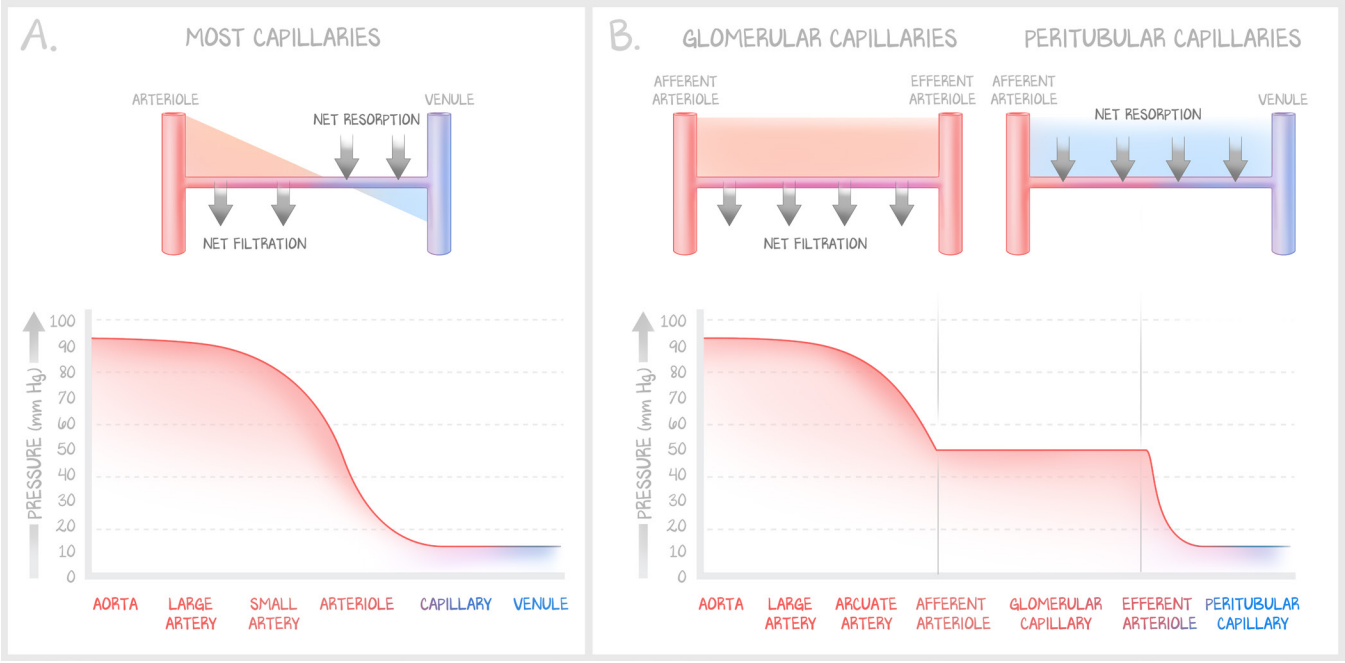


**Figure 3.4: Glomerular and Peritubular Capillaries Combined Mirror Normal Capillaries**
(a) A normal capillary bed. The arteriole drops the pressure from about 60 mmHg down to less than 20 mmHg. But at the end of the capillary bed, on the venule side, the hydrostatic forces have been depleted and the filtration force reverses, and fluid is reabsorbed from the tissue. (b) In the nephron circuit there is a similar arrangement, only divided between two capillary beds. Filtration occurs in the glomerular capillaries, where the afferent arteriole maintains an immense hydrostatic pressure and reabsorption occurs in the peritubular capillaries, where the efferent arteriole acts like every arteriole everywhere. The difference in the peritubular capillaries is that filtration has already occurred, so the oncotic forces that drive reabsorption are much greater than in normal capillaries.

This means that there is always going to be a strong driving force to filter fluid. This driving force, the hydrostatic pressure, is regulated by the afferent arteriole's attempt to maintain filtration at a constant rate—adapting to changes in systemic arterial pressure. It does this through a process called **autoregulation**. Autoregulation occurs both as a product of the stretch of a vessel in the kidney, called the myogenic response, and an osmolarity receptor that we will simplify, called tubuloglomerular feedback.

The **myogenic response** is induced by stretch of smooth muscle. Let's start with an afferent arteriole at rest, normal flow. The afferent arteriole has a baseline tone. Suddenly, the systemic blood pressure rises. More flow is directed at every capillary bed. The increased flow distends arteries, exerting an outward pressure on the vessel wall. The afferent arteriole is made up of the endothelial cells lining the vessel and the smooth muscle cells around the endothelial cells. As the vessel distends, the smooth muscles stretch. **Stretch-sensitive calcium channels** open, calcium flows into the cytoplasm, and those smooth muscles increase their tone. The afferent arteriole vasoconstricts. Constriction increases the resistance, keeping flow into the glomerular capillary the same. If there were less arterial pressure, the stretch would lessen, the calcium channels would lessen, smooth muscle contraction would lessen, and the afferent arteriole would dilate. This is a second-to-second mechanism that protects the glomerular capillary from varying pressure swings. It is also the same mechanism used by every arteriole everywhere.

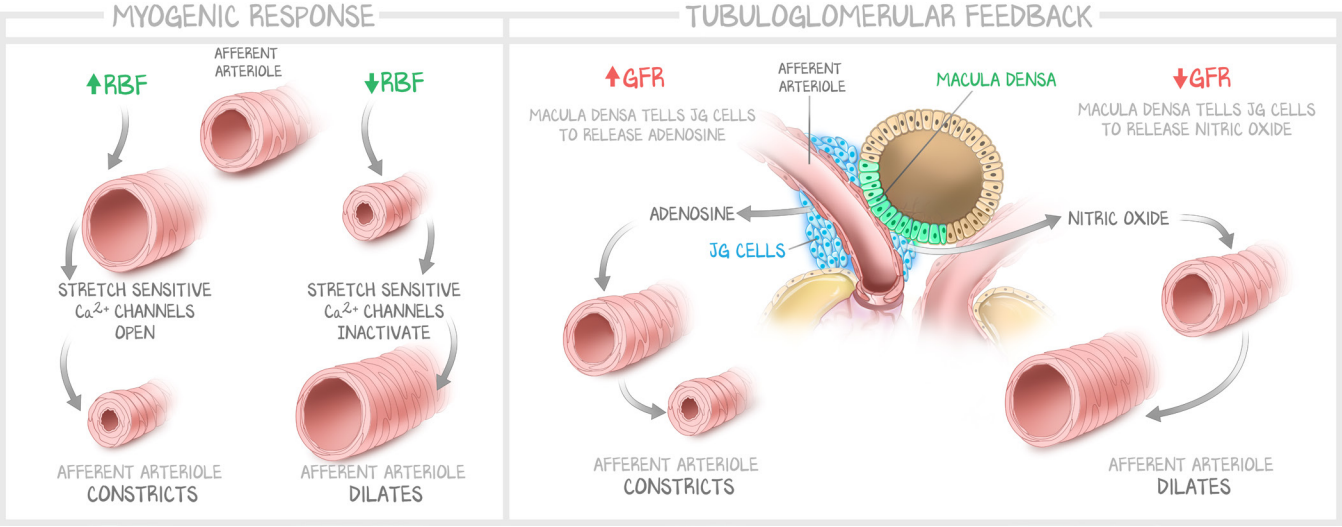


**Figure 3.5: Regulation of the Afferent Arteriole**
The myogenic response is regulated by stretch-gated calcium channels. It serves to maintain a constant hydrostatic pressure with varying RBF. Tubuloglomerular feedback is what regulates the afferent arteriole from within the kidney, the JG apparatus sensing GFR and influencing the afferent arterioles with adenosine and nitric oxide.

But the afferent arteriole is only sensing changing pressure coming into the glomerular capillary. It has no way of monitoring what's happening after the blood flows past the arteriole. That means the afferent arteriole is unaware of the glomerular filtration rate. Yet the afferent arteriole does adjust based on changes in glomerular filtration. The way it does that is by listening to the tubules, via tubuloglomerular feedback. Most tissues tell their arteriole they need more or less perfusion by using the molecules of metabolism—pH, $CO_2$, nitric oxide. The afferent arteriole can respond to those signals, but is mainly managed by the inputs from the JG apparatus.

**Tubuloglomerular feedback** is how the tubules of the **macula densa** assess the glomerular filtration rate and use the **JG cells** to tell the afferent arteriole what to do. What the macula densa is trying to assess is the glomerular filtration rate, assessing for a flow, a volume. The mechanism the macula densa uses to assess GFR is sodium. This is a fact. But it confuses learners because it suggests that changes in serum concentrations of sodium can impact the macula densa. They don't. The macula densa is a **flow sensor**. If there is too much flow, the macula densa signals the JG cells to release **adenosine**, which constricts the afferent arteriole, reducing GFR. If there is too little flow, the macula densa signals the JG cells to release **nitric oxide** to **dilate** the afferent arteriole.

But what about the efferent arteriole? In addition, if there is too little flow, the macula densa signals the JG cells to release **renin** as well. The output of renin is angiotensin 2. At the level of the glomerulus, angiotensin 2 constricts the efferent arteriole. Dilation of the of afferent arteriole brings more renal blood flow into the glomerular capillaries, brings more perfusion pressure. Constriction of the efferent arteriole drives that perfusion pressure to increase filtration. While the effect on the afferent arteriole is local, the effect of renin release to influence the efferent arteriole is systemic, with consequences discussed in the next section.

## The Katrina Switch

After Hurricane Katrina in New Orleans, Dr. Williams bought a house. It was a flip, and some of the light switches were installed upside down. Down was on and up was off. You have to remember that this isn't just a light switch—it's a Katrina switch. Down is on and up is off. As filtrate flows through the tubules it passes by the switch. The switch is loose and floppy, and it stays up by itself. If there isn't a good amount of flow through the tubule, the switch falls down, pulled by gravity. The default of the Katrina switch is be down, to be on. If there is a lot of flow through the tubules, the switch is pushed up, to off.

The Katrina switch is the macula densa. When the Katrina switch is on, there is low flow, low GFR. When the Katrina switch is on, the macula densa tries to increase GFR. It does this by having the JG cells release nitric oxide to dilate the afferent arteriole and by having the JG cells release renin. When the Katrina switch is off, there is good flow, a high GFR. Then the Katrina switch is flipped up, in the off position, the macula densa tries to decrease GFR. It does this by having the JG cells release adenosine and not release renin or nitric oxide.

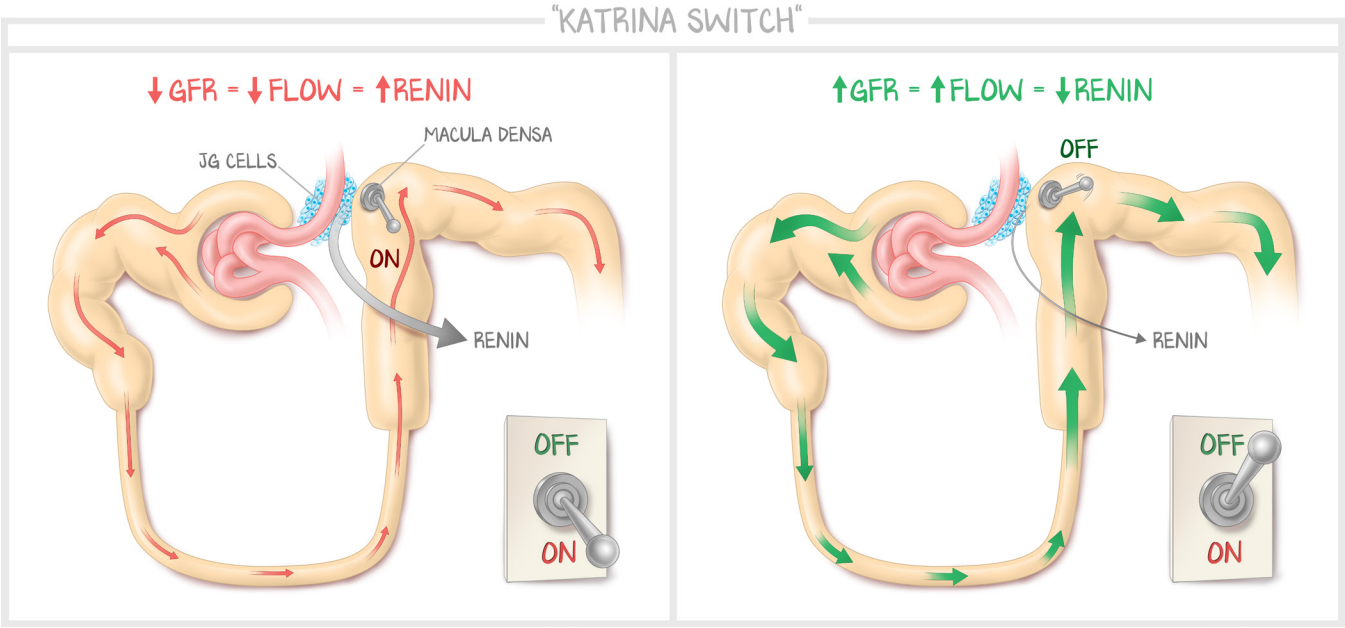


**Figure 3.6: The Katrina Switch**
A visualization of the Katrina switch as the teaching tool for how the macula densa acts as a flow sensor and how it acts as an effector of systemic hypertension. We've chosen to depict only the release of renin in relation to the switch's being on or off, so as not to convolute the illustration. This teaching tool is simple, but is immensely robust. You will see it used here in nephrology in the basic sciences, all the way through the intern content in internal medicine.

## Systemic Hydrostatic Pressure Regulation

This next section is included as a review of the renin-angiotensin-aldosterone axis as it pertains to systemic regulation of blood pressure. It is both a review from cardiology and a preview of the following lessons. Follow along with Figure 3.7 as you read.

The juxtaglomerular apparatus works through the afferent arteriole to regulate blood flow through its own glomerulus. All the JG apparatuses in concert influence the blood pressure of the human body. When the flow is low, the JG apparatus releases renin. **Renin** initiates the renin-angiotensin-aldosterone axis. We discussed this system and its global implications in Cardiology. We will keep this discussion focused mainly on the outcome of this system on the nephron.

The **renin-angiotensin-aldosterone system** (RAAS) is activated by a low-flow state in the tubules. The low-flow state in the tubules is used as a surrogate for perfusion pressure, and therefore systemic volume status. The kidney thinks that if there is a low GFR, it must be because there isn't enough volume in the body to perfuse the kidney. The problem with that, however, is that the macula densa doesn't assess renal perfusion pressures (tubular blood flow or renal plasma flow); the macula densa assesses GFR. When the macula densa senses a reduced flow, it disinhibits the JG cells, who release renin. Renin goes to the liver where it cleaves the -ogen from angiotensinogen to form angiotensin-1. Angiotensin-1 goes to the lungs where there is angiotensin-converting enzyme which makes angiotensin 2. Angiotensin 2 stimulates the adrenal cortex to make aldosterone. **Renin release by JG cells increases angiotensin 2 and aldosterone.**

**Angiotensin 2** "tenses the angios," inducing vasoconstriction everywhere, reducing the size of the tank needed to be filled by a reduced circulating volume. Angiotensin 2 directly affects the arterioles of the glomeruli as well as everywhere else. The net effect at the level of the arterioles is that **both afferent and efferent arterioles constrict**. Because the afferent arteriole has the myogenic response and the tubuloglomerular feedback from its own macula densa, but the efferent arteriole does not, the effect of angiotensin 2 on the afferent arteriole is weaker than on the efferent arteriole. That's how we got an improved GFR at the end of the last section. In an actual volume down state, angiotensin 2 both reduces the size of the tank and improves GFR. In a state where the macula densa senses a low flow, but the patient's volume status is normal, angiotensin 2 will induce vasoconstriction anyway, provoking hypertension.

**Aldosterone** increases sodium reabsorption in the collecting duct. Renin was released because the kidney thinks the body is volume-down. It acts to reduce the size of the tank (vasoconstriction) and also retain any volume to keep the tank filled. Aldosterone absorbs sodium in the collecting duct. Aquaporins, inserted by ADH, also stimulated by angiotensin 2 (Kidney #5: *Water*), reabsorb water. Water follows salt. Under the influence of aldosterone and ADH, the urine is concentrated and the water reabsorbed.

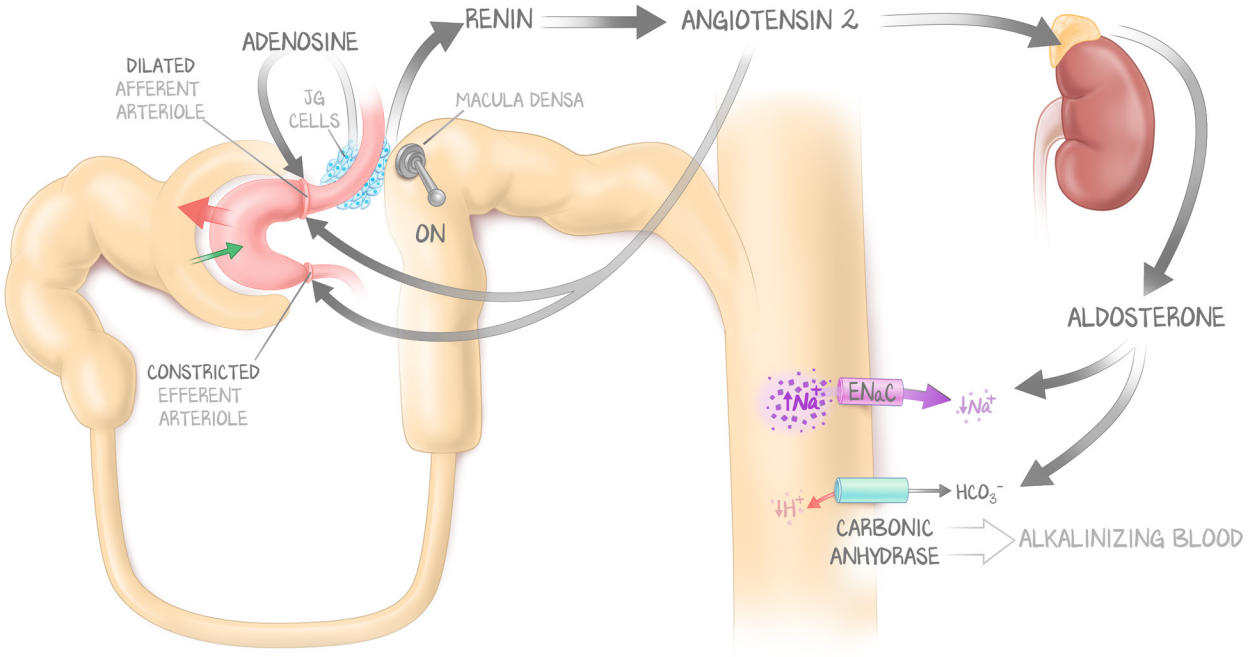


**Figure 3.7: Systemic Hydrostatic Pressure Regulation**
Follow along with this image as you read the text.